BLOOD TRANSFUSION IN PERNICIOUS ANEMIA

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DISCUSSION *by Arthur L. Bloomfield, San Francisco; Roy E. Thomas, Los Angeles; Ernest S. du Bray, San Francisco.*

A CRITICAL analysis of the status of blood transfusion in pernicious anemia is presented in order to emphasize certain limitations of this method of treatment, and not with the purpose of minimizing the usefulness and importance of this procedure. The question always comes up for consideration as soon as the diagnosis of pernicious anemia is established. The laity seems to have a general impression that blood transfusion is of lasting value, if not actually curative, in this disease, and too often the family and relatives of a patient press the physician in charge for early decision and action. What should be our attitude concerning this important question? Certain features of the disease must be borne in mind in helping to form a decision. An important fact to remember is that the anemia present is only one manifestation of the disease and the underlying cause of this anemia is unknown. A blood transfusion does not remove this underlying cause, and it seems quite probable that the underlying cause is little influenced in any manner by this procedure. It has never been clearly shown that transfusion prolongs the life of a patient with pernicious anemia.

Jones,[1] in a recent contribution states, "what appears to be a cure in an occasional patient can be brought about by repeated small transfusions of from 100 to 450 cc. of whole blood at four-day intervals." This article is characterized by a tone of optimism somewhat at variance with the opinion of clinicians of extensive experience, as Richard Cabot [2] and Billings.[3] To quote from Cabot, "I do not myself believe that the modern habit of treating pernicious anemia with transfusions prolongs life." Billings, in an interesting article on the present-day opportunities for the general practitioner, speaks as follows concerning pernicious anemia: "Under ordinary, good, rational management, with attention paid to the diet, the avoidance of fatigue and other hygienic measures, the patient's life will be conserved, as a rule, quite as long as if he submitted to all the modern measures practiced, including splenectomy and blood transfusions." Landis[4] distinctly condemns transfusion in pernicious anemia. He refers to Lichty's discussion on this subject in the *Therapeutic Gazette* (July, 1926). Lichty is of the opinion that such patients with transfusions will die sooner than those without, because each patient has a certain number of remissions to look forward to and transfusion simply hurries him through the entitled number of remissions. He admits, however, that in a case with immediate danger a transfusion may tide a patient over the crisis. Evans,[5] in his book on pernicious anemia just published, states: "If one expects too much from blood transfusion he will be disappointed. An analysis by Bloomfield to determine what benefit, if any, is to be derived from this method of treatment showed that life was not prolonged by it."

In order to appreciate the limitations of blood transfusion in the syndrome called pernicious anemia, we must enlarge our conception of this syndrome beyond the idea that it is due to a primary disease of the bone marrow, with all the symptoms secondary to the anemia present. We are, on the contrary, dealing with a systemic intoxication of widespread distribution involving at least the gastrointestinal tract, the nervous system, the liver, kidneys, and heart, as well as the blood-forming organs. The blood may not show any marrow disturbance until the disease has been present for some time, and only then, when the toxin or hemolytic agent begins to destroy blood cells in excess of the ability of the blood-forming organs to put out new cells. It is this hemolysis or destruction of the red cells, plus a depressing or inhibiting effect of the toxic agent on the bone marrow that causes the blood picture associated with the disease. This same blood picture is seen in certain cases of syphilis, of malignancy, and also in sprue. When a remission occurs in pernicious anemia the toxic agent is apparently neutralized or ceases to be formed, and then the bone marrow, left free to work unimpeded, seems to have plenty of materials and soon replenishes the circulating blood. If it has not been permanently damaged or crippled it may be able to regenerate an almost normal number of formed elements in the blood.

These remissions are fairly characteristic and constant in every case of pernicious anemia; just how they are brought about is not known. Our efforts at treatment are usually directed toward supporting a patient through a relapse until a remission occurs. Can transfusion during a relapse check the progress of such a relapse and bring about a remission? The evidence on this point is not entirely convincing because the mechanism of a remission is not understood. They occur without any treatment, and quite satisfactory remissions may occur after very serious relapses. Minot[6] expresses the opinion that the chances of a spontaneous remission occurring when a case is seen in relapse is in the vicinity of 35 per cent. Transfusion in all types of pernicious anemia taken together appears to bring about 10 to 20 per cent more remissions than occur spontaneously. One of our clinic cases was admitted to the Medical Service of the University of California Hospital in 1924, in coma and with pulse so feeble that he was considered "in extremis." He had been under observation about eighteen months and was found to have considerable hemolysis. At intervals during this period transfusions had been given with only slight temporary benefit. When he entered in such critical condition that it seemed only a matter of a few hours before the end, it was decided not to transfuse him. Instead of death during the night the morning brought some improvement, although he was delirious and very restless. By the third day, after admission, he was sitting up reading the news-

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paper and his bone marrow response was one of the most remarkable we have ever witnessed. The reticulated cells ran as high as 80 per cent of the total number of red cells. His remission was very satisfactory and lasted for over a year. This case is cited to show the difficulty in deciding just how much transfusions accomplish. Had we given this patient a transfusion it would have received much more credit than it deserved. The data at our disposal indicates that transfusion may assist in bringing about a remission and may, in some cases, check the progress of a relapse. There are no definite contraindications to transfusion except questionable compatibility of the blood. We know, however, that after several transfusions the recipient develops antibodies to the donor's blood and serious reactions may take place. Bowcock [7] has shown that the number of transfusions a patient may take are limited. At times, after ten or twelve transfusions, a recipient may develop agglutinins to the cells of any donor's blood. In such case one has to resort to intramuscular administration of blood. At times, after several transfusions, the recipient may develop antibodies or agglutinins for the donor's blood and the incompatibility may not show in the "blood-matching" tests. Then again, serious reactions will sometimes occur after proper grouping and "blood matching." These, fortunately, are very rare.

It seems unwise to give a transfusion in the face of active hemolysis, unless special features in the case demand it. A good index of hemolysis is the Van den Berg test in the serum or the Schleissenger test for urobilin in the urine. The intense, lemon-yellow color of the patient, with palpable enlargement of the spleen, are clinical evidences of increased hemolysis. Where hemolysis is active the blood from the transfusion may be destroyed in a short time. When a patient is extremely weak, with blood very low, it is a question of clinical judgment whether transfusion should be done, especially if the patient is seen for the first time. Even a slight reaction might be sufficient to cause a fatal termination.

When a cause is studied for the first time, and it is noted that the reticulated cells are above 2 per cent and are increasing, this may be taken as a sign that the marrow is actively regenerating. These reticulated red cells are readily brought out by staining a drop of fresh blood with .5 per cent alcoholic solution of brilliant creysl blue. Slides may be prepared by spreading the creysl blue on the slide and allowing the solution to evaporate, leaving the dry stain behind. These slides are kept on hand for use as desired. If, in addition to an increase of reticulated red cells, the proportion of neutrophyles is increasing, the eosinophylic proportion is rising, and the platelets increasing, a remission may be predicted, and it is sometimes better in the event of such evidence not to resort to transfusion. A sudden accession of transfused blood at such period may cause the marrow to cease its activity for a time. The physiological stimulus to the bone marrow of a marked deficit in the manner of red cells and hemoglobin is the greatest stimulus that can possibly be applied, and to have recourse to blood transfusion in the hope of stimulating still further the production of blood cells is too much like "whipping up" the tired horse who is already doing his utmost. A small transfusion of 200 or 300 cc. of whole blood may be of value after a remission is in progress, in furnishing the system with materials for building the stroma of red cells. Whipple [8] has emphasized the necessity for materials for building the stroma of cells in pernicious anemia. In transfusion the new blood may furnish complement and certain antibodies to neutralize the toxins present in the recipient's blood. When a patient is having distressing symptoms referable to the gastrointestinal tract, as vomiting, anorexia and diarrhea, and is extremely weak and dyspnoeic, a transfusion may alleviate these symptoms and make for greater comfort. There seems also to be some evidence that the remissions occurring after transfusion may be of longer duration and of somewhat better character as to the patient's general condition and strength than where transfusion is not employed. This is especially true where previous remissions have not been of a satisfactory character. There is a definite place for transfusions in the treatment of pernicious anemia, but they should not be used before a carefully worked out diagnosis has been made and they should never be given without thoughtful consideration as to the needs of the patient. The possibility of an unsatisfactory result should be explained to those responsible for the care of the patient. There seems to be a justifiable hope that the treatment of pernicious anemia by diet, as recommended by Minot,[9] will cut down the need for transfusion. The ability to bring on a remission by means of this special diet, obviating the necessity of transfusions, would constitute a distinct advance in treatment of this disease.

SUMMARY

There is no convincing evidence that transfusions prolong the life of a patient with pernicious anemia. They may be employed to bring on or hasten a remission, especially when the clinical progress of the patient is more or less stationary. It is probably better when a remission is imminent not to give a transfusion, as this may have the effect of slowing up the efforts of the bone marrow. It should be remembered that the number of transfusions which a given patient may take is limited, therefore they should not be used without some definite indications.

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DISCUSSION

ARTHUR L. BLOOMFIELD, M. D. (Stanford Medical School, San Francisco)—I am quite in accord with the general results of Doctor Falconer's paper.

Some years ago we analyzed [1] very carefully the re-

1. Bulletin Johns Hopkins Hospital, 1918, Vol. 29, p. 101.

sults of transfusion of blood in twenty-six patients with pernicious anemia who were followed over long periods of time. One hundred and one transfusions were given and individual patients received from one to seventeen, the largest total amount of blood being 8700 cc. and the smallest 300 cc. The single transfusions varied in amount from 300 to 900 cc. The results of this analysis brought out no evidence that the total duration of life was prolonged by the treatment, nor did transfusions seem to be of definite value as an emergency measure in tiding patients over at a time when the blood count was very low. Of nine patients entering the hospital with blood counts of under a million and receiving transfusion, six improved and left the hospital and three, or 33 1/3 per cent, died; whereas of ten other patients with counts under a million who did not receive transfusion, eight improved and two, or 20 per cent, died.

The most important conclusion seemed to be that the time when transfusion is done is of particular importance. If the patient is in a refractory state, which is usually the case during the relapse, transfusion seems to have little effect. On the other hand, if performed at a time when the patient was not refractory (i. e., when spontaneous remission was imminent or had commenced), improvement seemed to be brought on in about one-half the cases, and it was possible to raise the blood count to a higher level than it usually reaches spontaneously. Such artificial plethoras did not increase the duration of the remission, although the patients usually had a sense of well-being while the count was high.

As Falconer points out, the anemia is evidently only one of a number of harmful effects which are produced by whatever agent is responsible for pernicious anemia, and it is quite obvious that transfusions at best can do no more than aid in temporary improvement in selected cases.

ROY E. THOMAS, M. D. (1136 West Sixth Street, Los Angeles)—In the treatment of any disease it is difficult to see how the patient can be permanently benefited by a therapeutic measure directed against one of its symptoms.

Falconer has clearly shown in his paper that transfusion of blood does not materially prolong life in the great majority of cases of pernicious anemia in which it is used. He has gone a step further and given theoretical reasons for believing that no better results could be expected.

For obvious reasons it is particularly difficult to determine the value of any therapeutic measure in a disease which is characterized by spontaneous remissions. Only by such careful blood studies as Falconer has made can the reaction of the bone marrow to transfusions in pernicious anemia be determined and thus enable us to avoid their use when they are likely to prove of no benefit or even harmful.

I do not believe we are ready to dispense entirely with transfusions in pernicious anemia. Falconer states that they bring about 10 to 20 per cent more remissions than occur spontaneously. If this is true life is probably prolonged in some instances, for Lichty's view that every case of pernicious anemia has just so many remissions to look forward to seems absurd. Also many times transfusions seem to add much to the comfort of the patient and are thus quite worth while.

However, I have recently had the opportunity to observe for a considerable period three cases of pernicious anemia which had presented symptoms of the disease for 8, 12, and 15 years, respectively. One had a splenectomy followed by hydrochloric acid in large doses. The second had many transfusions which seemed to add much to her comfort. The third who has had neither splenectomy nor transfusions is the only one left alive to eat liver.

ERNEST S. DU BRAY, M. D. (University of California Medical School, San Francisco)—Falconer's timely warning about the thoughtless use of blood transfusion in the treatment of pernicious anemia is but a reflection of the opinion of many of the most careful students of the hematopoietic diseases. He has defined quite clearly the limitations of its use and at the same time he indicates certain pitfalls which may attend the method. It is pleasing to see that he stresses the point that the decision for or against transfusion is frequently a matter which demands extremely sound clinical judgment. Another important phase which he mentions and which I feel is worth re-emphasizing is the possibility of a severe reaction in a patient who, because of repeated transfusions, has developed antibodies for compatible bloods. It is now agreed that transfusion never cures pernicious anemia, and the patients in whom the best results are obtained are those who are most likely to have a spontaneous remission and who react best to any treatment. The procedure must be regarded as a useful and often effective method for the alleviation of distressing subjective symptoms, and in rare and carefully selected cases may even be a life-saving measure.

CHRONIC APPENDICITIS

A STUDY OF 202 CONSECUTIVE CASES

By HERSEL E. BUTKA *

"THERE are two types of appendicitis," says one author, "one acute, and the other for revenue only," while some others ask the question, "Is chronic appendicitis a myth?"

Investigators are at variance as to the pathological findings in chronic appendicitis. Ribberts states that the normal appendix is always empty, while Aschoff claims that 62 per cent of normal appendices contain feces. Roentgen ray examination shows that the appendix fills, empties, and alters its shape periodically. There may be pathological conditions present that cannot be proved by the anatomist or histologist, but can be demonstrated roentgenologically by the finding of a large open canal which fills easily but is unable to properly empty and retains this material over long periods of time.

The rôle of hard fecal material and foreign bodies in the pathogenesis of chronic appendicitis is somewhat disputed, but probably should be recognized. Because of the well-known frequency of these bodies in acute appendicitis, their presence will be considered proof of chronic appendicitis in this paper.

Eastman states that many cases of so-called chronic appendicitis must be considered as due to malposition, adhesions and kinks, with little microscopic pathology. Aschoff's description of changes in chronic appendicitis enumerates the findings briefly as "stenosis, induration of wall, retention of mucus, fecal masses, adhesions and kinking." He believes that chronic appendicitis is never primary but is always due to a previous acute attack or attacks, many times occurring during childhood and simply called "stomach ache."

According to Mallory, "during repair, the appendix is often infiltrated with numerous eosinophiles, and the lymph vessels filled with lymphocytes. The appearance presented by appendices in the various stages of repair is often spoken of as chronic appendicitis, but this term is not justified."

The microscopic appearance of the appendix varies normally. The coats vary in thickness with age. Lymphoid tissue is greatest in the young, while

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